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CERTIFICATE

This certificate is issued in support of an application for Patent registration in a country outside New Zealand pursuant to the Patents Act 1953 and the Regulations thereunder.

I hereby certify that annexed is a true copy of the Provisional Specification as filed on 11 June 1999 with an application for Letters Patent number 336241 made by DEC INTERNATIONAL NZ LIMITED.

I further certify that pursuant to a claim filed on 19 August 1999 under Section 24(1) of the Patents Act 1953, a direction that the application proceed in the name of DEC RESEARCH.

Dated 14 June 2000.

Neville Harris
Commissioner of Patents

COMMISSIONER OF PATENTS, TRADE MARKS & DESIGNS
NEW ZEALAND

NEW ZEALAND

PATENTS ACT, 1953

336241

PROVISIONAL SPECIFICATION

"Devices for the Delivery of a Liquid Vehicle"

We, **DEC INTERNATIONAL NZ LIMITED**, a company duly incorporated under the laws of New Zealand of 558 Te Rapa Road, Hamilton, New Zealand, do hereby declare this invention to be described in the following statement:

The present invention relates to improvements in the delivery of an active agent into an environment (whether *in vivo* or *in vitro*) and particularly, although not solely, to devices having application in the delivery of one or more active ingredients into a mammal (eg; intra ruminally or intra vaginally) or into an aqueous environment, e.g. an aquarium.

In our PCT/NZ98/00011 we disclose in some detail the background to the passive and active release of active ingredient(s) into the body cavity of mammals including the vaginal tract and the rumen.

A problem discussed in such specification is the release profile of a substance delivery device whether for a body cavity or otherwise (for example, a liquid body such as an aquarium) arising from a passive leakage of material which can affect the overall release profile.

We have investigated different known procedures of active release and have considered new procedures insofar as the means of expression of a liquid vehicle from a reservoir of reducible volume is concerned. It is to such substance delivery devices and their use that the present invention is directed.

In a first aspect the present invention consists in **a delivery device** comprising or including

means defining a reservoir (hereafter "reservoir means") for a liquid vehicle, said reservoir means having an outlet through which the liquid vehicle in use is to be expressed,

expressing means to reduce the available volume for the liquid vehicle within said reservoir means under the action of a gas in use to be or being generated, and

means to generate a gas so as to cause said expressing means to express the liquid vehicle out of said outlet, such gas generation arising from either or both the gaseous emission from a battery forming part of an electrical circuit and/or the gaseous emission from an electrolysis cell (for example of a hydrogel) energisable by an electrical circuit.

In one aspect of the present invention said expressing means to reduce the volume of the reservoir of said reservoir means is a balloon or membrane that inflates with the gaseous emission(s) to express the liquid vehicle interposed between it and a wall or walls of the reservoir and said outlet.

In another form of the present invention said expressing means to reduce the volume of said reservoir is a piston, the piston itself being moved directly or indirectly by the gaseous emission(s).

Preferably the gaseous omission is generated by the use of a battery of a kind typified by US Patent 5,242,565. In other forms the electrolysis cell option may be utilised and is typified by, for example, US Patent 5,352,464.

In a further aspect the present invention consists in **a substance delivery device** having means of variable geometry or dense means to facilitate retention in a body cavity selected from the vaginal tract and the rumen, said device otherwise being a device as previously defined.

In still a further aspect the present invention consists in a delivery device comprising or including

means defining a reservoir (hereafter "reservoir means") for a liquid vehicle, said reservoir means having an outlet through which the liquid vehicle in use is to be expressed,

inflatable means to reduce the available volume for the liquid vehicle within said reservoir means under the action of a gas in use to be or being generated to inflate said inflatable means,

means to generate a gas so as to cause said inflate means to inflate to express the liquid vehicle out of said outlet.

Preferably said gas generation arises from either or both the gaseous omission from a battery forming part of an electrical circuit and/or the gaseous omission from an electrolysis cell (for example, of a hydrogel) energisible by an electrical circuit.

In still another aspect the present invention consists in a delivery device comprising or including

means defining a reservoir (hereafter "reservoir means") for a liquid vehicle, said reservoir means having an outlet through which the liquid vehicle in use is to be expressed,

an expressing piston to reduce the available volume for the liquid vehicle within said reservoir means under the action of a gas in use to be or being generated, and

means to generate a gas so as to cause said expressing means to express the liquid vehicle out of said outlet,

wherein said liquid vehicle in respect of said outlet is of water and progesterone.

Preferably the gas generation arises from either or both the gaseous omission from a battery forming part of an electrical circuit and/or the gaseous omission from an electrolysis cell (for example, of a hydrogel) energisible by an electrical circuit.

Preferably said means to generate gas in respect of reservoir means of initial volume of from 5 to 100 ml where the reservoir means is in the form of a barrel of the equivalent of a cross-sectional area to piston stroke ratio of from 5 to 100 ml is of hydrogen gas if measured at normal atmospheric conditions and sea level.

Preferably each form of the present invention includes switching means of some appropriate type (whether manual or automatic) or indeed circuit completion means which initiates action.

Preferably a resistor or a known or preset resistance is provided to control the gas release profile whether under the control of the microprocessor or not (preferably not).

In a further aspect the present invention consists in a device in accordance with any one of the previous definitions thereof wherein said liquid vehicle is water or ethanol or benzyl alcohol etc.

In still other aspects the present invention consists in a method of providing a delayed release of a liquid vehicle in to a body cavity of a mammal or in to a liquid environment or other environment which comprises the operative use of a plunger form embodiment of a delivery device in accordance with the present invention.

In still another aspect the present invention consists in a method of providing fast release of a liquid vehicle in to a body cavity of a mammal or in to any liquid environment which comprises the operative use of a delivery device in accordance with the present invention where the expressing means is an inflatable means inflatable directly by the gas being generated.

Preferably said devices do not include a dip tube or the equivalent of a kind as defined in, for example, PCT/NZ98/00011.

In still a further aspect the present invention consists in an intra ruminal device which is also a delivery device in accordance with the present invention.

In still a further aspect the present invention consists in an intra vaginal device which is also a delivery device in accordance with the present invention.

In still a further aspect the present invention consists in a method of providing an active release of a liquid vehicle greatly in excess of any passive release of the liquid vehicle which comprises positioning in to an appropriate body cavity of the mammal a delivery device in accordance with the present invention where the means to express the liquid vehicle and/or to reduce the volume available for the liquid vehicle in the reservoir means is a piston, the means to generate the gas and the relationship of the piston to its barrel or the equivalent and the outlet is such as to confer an initial delay in out feed but thereafter under sustained gas generation and increasing incremental or continuous release of the liquid vehicle under the movement of the piston.

As used herein piston encompasses any plunger type arrangement where the syringe like will not.

In still a further aspect the present invention consists in any of the devices or apparatus previously defined whereby means is provided to enable for equalisation of pressures between the zone externally adjacent said outlet with some region of the device having a closer access to ambient condition when the device is retained in a body cavity, such means providing for fluid (preferably gas and preferably air) communication to minimise pressure differentials adjacent the outlet as a result of movement of walls of the

body cavity and an air seal about the device in the body cavity.

Preferably the arrangement is of any kind typified by the diagrammatic form shown in, for example, Figure 5.

This invention may also be said broadly to consist in the parts, elements and features referred to or indicated in the specification of the application, individually or collectively, and any or all combinations of any two or more of said parts, elements or features, and where specific integers are mentioned herein which have known equivalents in the art to which this invention relates, such known equivalents are deemed to be incorporated herein as if individually set forth.

The invention consists in the foregoing and also envisages constructions of which the following gives examples.

Preferred forms of the present invention will now be described with reference to the accompanying drawings in which;

Figure 1A shows a balloon or membrane containing embodiment of a device,

Figure 1B is a piston including syringe-like embodiment,

Figure 2 is a plot for the Figure 1A and B embodiments of volume released against time,

Figure 3 compares for the Figures 1A device the *in vivo* and *in vitro* delivery profiles with a plot of volume release against time,

Figure 4 is a similar comparison for the Figure 1B device plotted in a similar fashion to that of Figure 3, and

Figure 5 shows how (in this case for the more energy demanding but better *in vivo* delivery profile device - that of Figure 1B) the transient pressure differentials (eg; the vaginal tract) adjacent the outlet may better.

The present invention recognises advantages that might flow to particularly body cavity retainable devices (eg; intra vaginal or intra ruminal devices) where a liquid vehicle is to be actively released and there is a desire to reduce the ratio of passive release to active release. In this respect embodiments to be discussed hereinafter recognise advantages that arise from the use of gas generation for the purposes of reducing the available volume in a reservoir for the liquid vehicle to be expressed.

For low energy usage preferably an inflatable device as hereinafter described by reference to Figure 1 is preferred yet surprisingly as will hereinafter be described we have determined that a plunger or piston like reservoir reduction provides a better *in vivo* release profile over that of the inflation option owing to a reduction in passive delivery. Where therefore rapid release with some passive content is not of concern significant energy savings are available for an active release device utilising the inflation option. Where however controlled release is of primary importance and/or there is no concern

with an initial startup delay or a startup delay is desired the option hereinafter described by reference to Figure 1B with the use of a gas generated battery is to be preferred even though it will be a higher energy requirement for such an option.

The devices of Figures 1A and 1B utilize electronically controlled gas to facilitate the delivery of a vehicle. The vehicle may be aqueous, organic or non-organic based. The production of gas may be from a suitable electrolytic material (US5352464) or galvanic cell (US 5242565) and is controlled by suitable circuitry.

The device of Figure 1A incorporates a balloon that upon the production of gas and its movement into the balloon means the balloon expands to fill the reservoir containing the liquid vehicle. This expansion results in the delivery of the liquid vehicle out of the outlet.

The device of Figure 1B incorporates a piston that upon the production of gas behind the piston results in its migration towards the outlet. This forward migration results in the delivery of the liquid vehicle.

In Figure 1A the balloon 1 is disposed within a syringe like reservoir 2 having an outlet 3. The liquid vehicle 4 is interposed between the walls of the reservoir 2 the outlet 3 and the balloon 1 so that inflation thereof will have the effect of expressing the liquid vehicle 4 out of the outlet 3. The inflation is by means of electronic gas production at 5 which feeds gas via an appropriate conduit 6 to the confines of the balloon or diaphragm 1. Such conduit is indicated as 6. The arrangement as in Figure 1B is much the same save that instead of the balloon or membrane 1 a piston 7 is provided which will move to reduce the volume for the liquid vehicle 4 and oppose there between and the outlet 3.

In use when both devices of Figures 1A and 1B are operated with the same rate of gas production the arrangement as shown in Figure 1A with the inflatable balloon allows for a more rapid onset of delivery with a greater flow of vehicle compared to the piston arrangement which is characterised by a lag in the onset of delivery and a reduced delivery rate.

Accordingly for some applications the device of Figure 1 offers advantages over a device of Figure 1B. In the plot of Figure 2, the lag in the onset of delivery from the configuration of Figure 1B is readily apparent from the lower line on the graph,

Preferably the control circuitry involves a resistor (variable or otherwise) of an appropriate kind to affect the current flow. The circuitry may optionally be microprocessor controlled.

The liquid vehicle is preferably at least primarily aqueous, organic or non-organic as far as its liquid content is concerned. Whilst in preferred forms the vehicle as a whole may be viewed overall as a liquid it need not necessarily be a solution. The liquid itself may be the active or merely a liquid carrier for the active elsewhere in the vehicle.

Accordingly, the term "liquid vehicle" should be interpreted as including any one or more of a suspension, a dispersion, an emulsion, a susproemulsion, a solution and the like.

Whilst the arrangement of Figure 1A has definite efficiencies in respect of the energisation required for the purpose of gas generation per volume of liquid vehicle dispensed and the lack of delay in such dispensation, the device of a kind shown in Figure 1B has been found to improve the delivery of liquid vehicle whilst inserted into a body cavity such as the rumen or the vaginal cavity.

Figure 3 shows a plot of liquid vehicle delivered in grams against time and days with a device as depicted in Figure 1A. The straighter line is the in vitro delivery of vehicle from a device of Figure 1A whilst the more curved line represents the in vivo delivery profile for an identical device. It is therefore surprising that whilst a device as shown in Figure 1A has the comparative in vitro/in vivo profiles shown in Figure 3, that a device as shown in Figure 1B has more agreement between the in vitro/in vivo profiles. In this respect see Figure 4 where in a similar way to that of Figure 3 the comparative performance of a device as in Figure 1B is shown in the in vitro and in vivo delivery modes. That line indicated with the shaded squares represents the in vivo profile. For the purpose of the generation of the data shown in Figures 3 and 4 the volume of liquid vehicle being dispensed was in each case water to be expressed out of a 2 mm diameter outlet. In each case the syringe like reservoir was of a cylindrical form and was powered over the duration of the comparative trials by a galvanic cell of the kind disclosed in US Patent 5242565 capable of generating over the life of the cell to depletion up to 180 ml of hydrogen when measured at normal atmospheric conditions at sea level.

Figure 5 shows a variation of the device as shown in Figure 1A. In this form means is provided to reduce variations at least over the medium term in the pressure differential in a body cavity with that of the ambient atmosphere. For this purpose a tube 8 is provided which in the case of an intra vaginal device as shown in Figure 5 (the variable geometry wings not being shown for convenience, but do see our PCT/NZ97/00052 (published as WO97/40776) it is possible for the tube 8 which may serve in part as a withdrawal mechanism for the device a passageway 9 through to an outlet zone 10. Experimentation with, for example, cattle has shown in the short to medium terms significant fluctuations in the pressure about the outlet of devices of the kind shown in Figures 1A and 1B which have the effect of providing a different net force acting on the liquid vehicle yet to be expressed. This is particularly disadvantageous with the device of Figure 1A where there is (as demonstrated in Figure 2) a more rapid onset of delivery following any adjustment in pressure on the liquid vehicle.

Accordingly, whilst the device of Figure 1B has a better profile under variations

of pressure, an arrangement that seeks to reduce localised pressure variations externally of the device but adjacent to the outlet must be viewed as a mechanism ensuring a better and more predictable delivery profile.

Description of the technology:

The devices depicted in Figures 1A and 1B utilize electronically controlled gas **5** to facilitate the delivery of a vehicle. The vehicle may be aqueous, organic or non-organic based. The production of gas may be from a suitable electrolytic material (US 5354264) or galvanic cell (US 5242565) and is controlled by suitable circuitry.

The top device of Figure 1A incorporates a balloon that upon the production of gas within **6** the balloon **1** expands to fill the reservoir **2** containing a vehicle **4**. This expansion results in the delivery of the liquid vehicle out of the outlet **3**.

The bottom device of Figure 1B incorporates a piston **7** that upon the production of gas behind **6** the piston results in its migration towards the outlet. This forward migration results in the delivery of vehicle.

Figure 3 shows both the in vitro and in vivo delivery of vehicle from a body cavity for the device of Figure 1A.

Figure 4 shows the in vitro and in vivo agreement of vehicle delivered for the device of Figure 1B.

The device of Figure 5 utilizes electronically controlled gas to facilitate the delivery of a vehicle. The vehicle may be aqueous, organic or non-organic based. The production of gas may be from a suitable electrolytic material (US 5354264) or galvanic cell (US 5242565) and is controlled by suitable circuitry.

The device of Figure 5 shows improvements to enable a more controlled delivery of vehicle to a body cavity. The addition of a tube **9** facilitates the maintenance of a constant pressure within the cavity **10** in relation to the exterior pressure **8**.

DATED THIS 11th DAY OF June 1999
A.J. PARK & SON
PER
AGENTS FOR THE APPLICANT

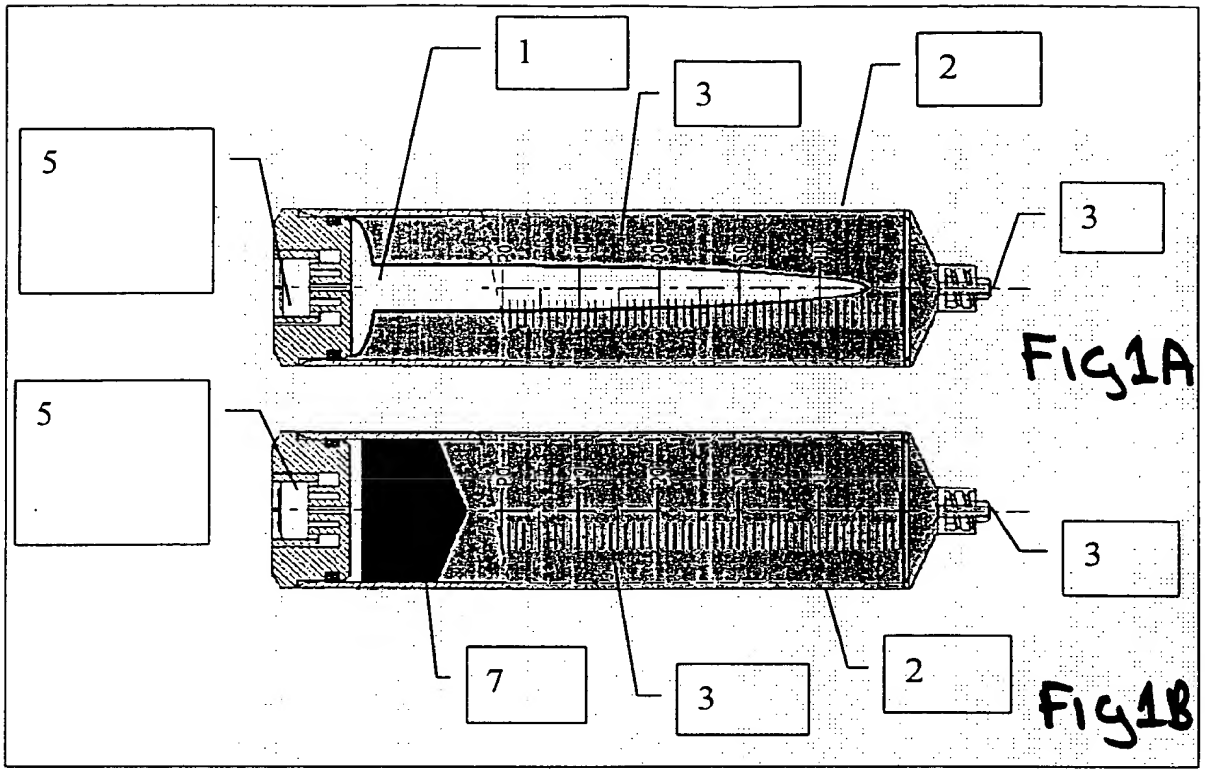

Fig1A

Fig1B

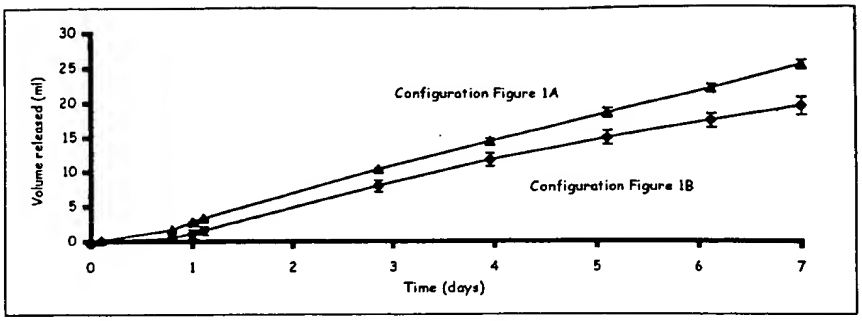

Figure 2. Delivery of vehicle from a balloon type device (configuration Figure 1A) compared to a piston type device (configuration Figure 1B). Both devices are operating with the same rate of gas production, note the lag in onset of delivery for configuration Figure 1B is greater than for configuration I. Error bars are standard error means (n=3).

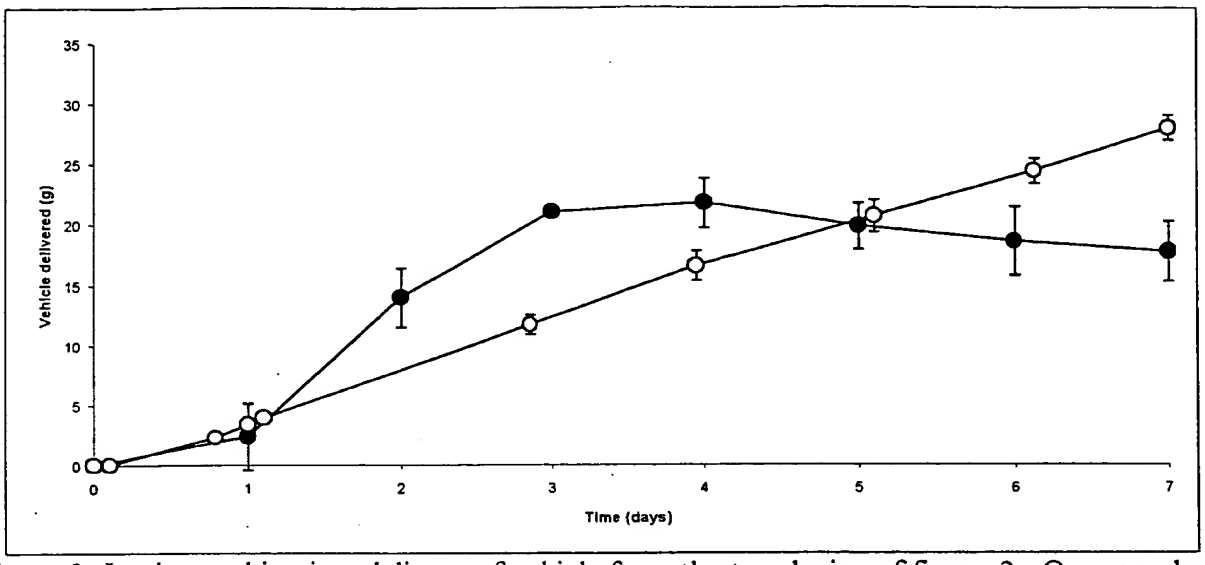

Figure 3. In vivo and in vitro delivery of vehicle from the top device of figure 3. Open symbols represent in vitro delivery profiles; closed symbols represent in vivo delivery profiles. Error bars are standard error means (n=3).

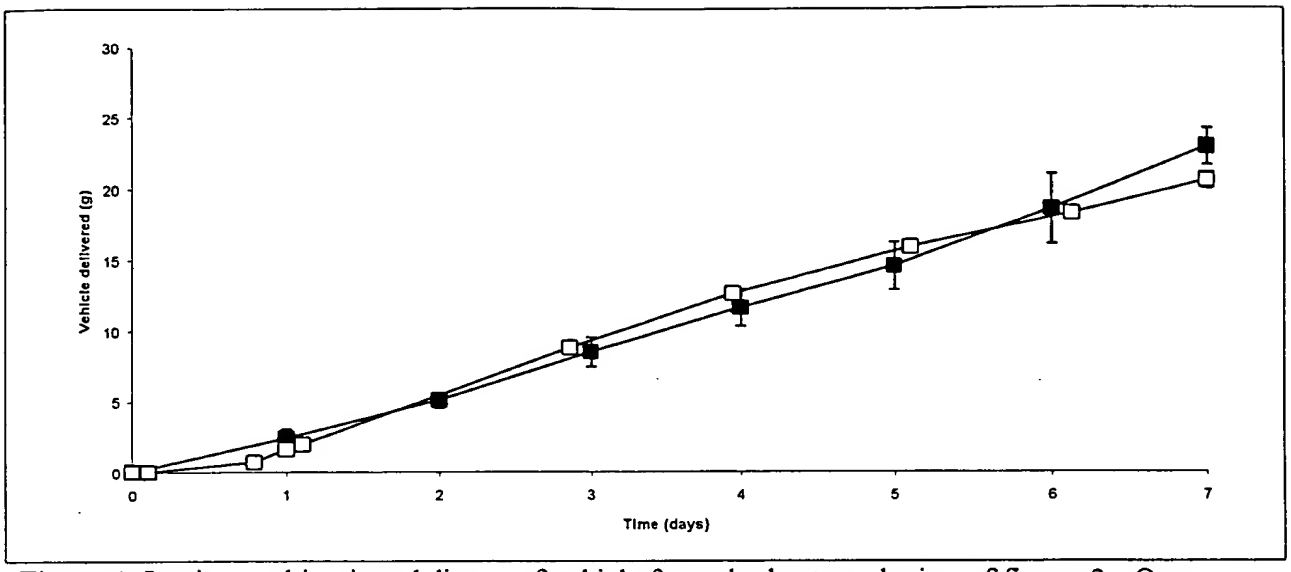

Figure 4. In vivo and in vitro delivery of vehicle from the bottom device of figure 3. Open symbols represent in vitro delivery profiles; closed symbols represent in vivo delivery profiles. Error bars are standard error means (n=3).

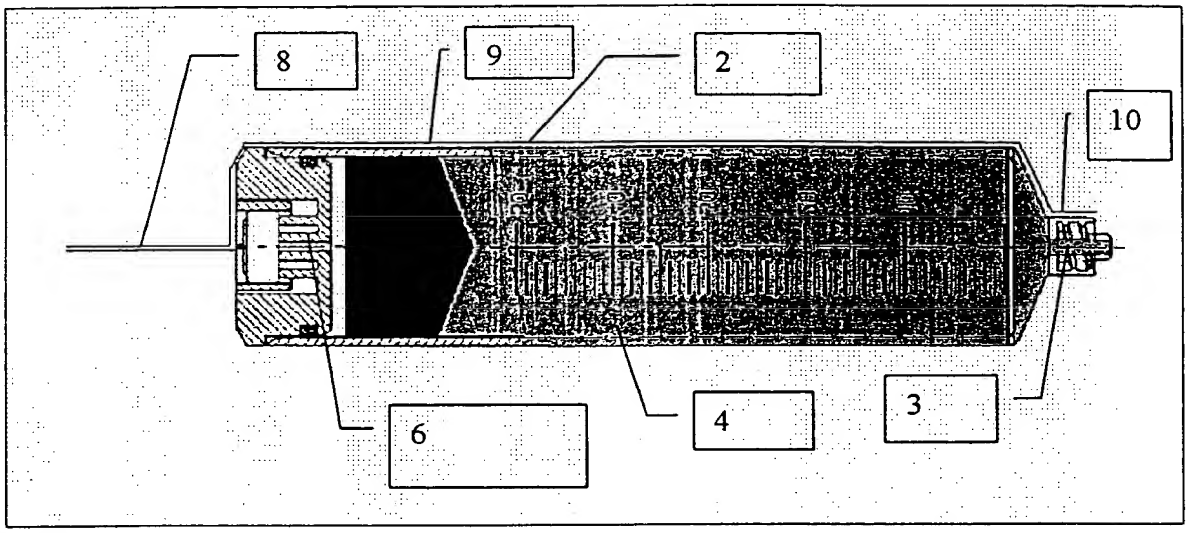

Figure 5.